Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-6 and 11-16 are pending in the application, with claims 1 and 11 being the independent claims. Claim 11 is sought to be amended by the present amendment. This change is believed to introduce no new matter, and its entry is respectfully requested.

Claim 11 has been amended to put the claim into better condition for allowance by correcting an obvious error. The amendment to claim 11 was not made earlier because Applicants did not detect this error until now. Specifically, claim 11, at line 4, has been amended to delete the phrase "of a full-length separase," so that the claim recites that the active separase, optionally upon activation in the presence of securin, is incubated in the presence of a separase substrate with a test compound. Support for this amendment can be found in the specification, e.g., at page 8, lines 23-26; at page 10, lines 7-8; and in claim 1 and claim 3, as originally filed.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

A. Enablement

Claims 1-5 and 11-15 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. (Office Action, page 2). Applicants respectfully traverse this rejection for the reasons set forth in the previous responses and provide the following additional remarks.

First, in justifying the rejection, the Examiner has ignored the functional limitation of the claims. According to the Examiner:

> [T]he nature and breadth of the claims encompass any method for identifying a test compound that inhibits the proteolytic activity of a separase using any substrate peptide comprising an amino acid sequence EXXR, wherein X is any amino acid. The examiner takes the position that these separase substrates containing EXXR encompass any peptide comprising any number of amino acid residues including modified and non-naturally occurring amino acid residues.

(Office Action, page 2). The independent claims, however, specify that the separase substrate is capable of being cleaved by the active separase. As explained in Applicants' previous replies, a person of ordinary skill in the art would have been able to easily determine through routine screening which peptides comprising the amino acid sequence EXXR are capable of being cleaved by active separase. (*See, e.g.*, Reply Under 35 U.S.C. § 1.111, filed on February 9, 2006, pages 4-7). Thus, contrary to the Examiner's assertion, the claims do not encompass methods that involve the use of *any* peptide comprising the amino acid sequence EXXR. To the extent that the rejection is based on this erroneous interpretation of the breath of the claims, the rejection is in error and should be withdrawn.

The Examiner next presented comments regarding the length and composition of the separase substrates used in the practice of the claimed methods. In particular, the Examiner stated that:

> The specification does not provide any guidance or prediction on how the length or the composition of the peptide containing EXXR would affect the ability of the separase to recognize and hydrolyzes [sic] the peptide. The specification does not provide any indication where EXXR should be in relation to the N- or C-terminal of the

> peptide which will enable the separase to recognize and hydrolyze the peptide. It is not clear from the specification if large peptide comprising EXXR would be hydrolyzed by separase since the specification discloses that small peptides consisting of SEQ ID NO:9, SEQ ID NO: 11, or SEQ ID NO: 12 were found to be separase substrates.

(Office Action, pages 2-3). This explanation falls far short of establishing a *prima facie* case of lack of enablement. According to the MPEP, the minimal requirement for establishing a *prima facie* case of lack of enablement is for the Examiner to "give reasons for the uncertainty of the enablement." M.P.E.P. § 2164.04. The Examiner here has not presented any evidence or sound scientific reasoning to suggest that the length of a peptide containing the separase cleavage motif EXXR, or the position of the EXXR motif relative to the N- and C-termini of the peptide, would influence the peptide's ability to be cleaved by separase. In addition, the Examiner has not presented any evidence to suggest that a person of ordinary skill in the art would have had any difficulty in ascertaining the appropriate sizes of EXXR-containing peptides that could be used in the practice of the claimed methods. Nor has the Examiner presented any evidence to suggest that a person of ordinary skill in the art would have had any difficulty in ascertaining the appropriate positions of the EXXR motif relative to the N- and C-termini of a peptide that would permit the peptide to be recognized and cleaved by a separase. In fact, Applicants submit that persons of ordinary skill in the art, at the time of the effective filing date of the present application, were able to routinely make and test a wide variety of polypeptide substrates for their ability to be cleaved by separase. (*See, e.g.*, Supplemental Reply filed on June 14, 2005, pages 5-7). No evidence has been presented to contradict Applicants' position on this point.

With regard to the Examiner's statement, that "[i]t is not clear from the specification if large peptides comprising EXXR would be hydrolyzed by separase . . .," the Examiner's attention is directed to the Examples in the specification which demonstrate the cleavage of the full-length SCC1 protein (which contains an EXXR motif) by separase. (*See, e.g.*, Example 1, pages 18-20, and Fig. 1, demonstrating the cleavage of a Myc-tagged SCC1 protein). The Examples of the specification therefore provide clear evidence that full-length proteins containing the EXXR motif are capable of being cleaved by separase. By contrast, the Examiner has failed to provide *any* evidence suggesting that the size or composition of a peptide comprising the EXXR motif would adversely effect its ability to be cleaved by separase.

In the previous response, Applicants pointed to two exemplary references describing methods for screening and identifying enzyme substrates. (*See* Reply Under 35 U.S.C. § 1.111, filed on February 9, 2006, pages 4-5, citing Smith *et al.* and Cryns *et al.*). As noted by Applicants, Methods such as those set forth in Smith *et al.* and Cryns *et al.* could have been used by persons of ordinary skill in the art to identify separase substrates for use in the practice of the currently claimed methods. The Examiner has not presented any argument or evidence to contradict this assertion. The Examiner simply stated that:

> While the cited references of Smith et al. and Cryns et al. describe general methods for searching and screening for protease substrates, the prior art does not provide guidance or prediction on whether any peptide comprising EXXR and any number of amino acid residues including modified and non-naturally occurring amino acid residues would be hydrolyzed by separase.

(Office Action, page 3). Thus, the Examiner has acknowledged that Smith *et al.* and Cryns *et al.* show that methods for screening for protease substrates were generally known in the art. Significantly, the Examiner has failed to explain why methods such as those that were successfully used in Smith *et al.* and Cryns *et al.* could not have likewise been successfully used to identify separase substrates for use with the currently claimed methods.

The Examiner, in justifying the rejection, has referred to what the prior art allegedly *does not* show. For Example, according to the Examiner, "the prior art does not provide guidance or prediction on whether any peptide comprising EXXR and any number of amino acid residues including modified and non-naturally occurring amino acid residues would be hydrolyzed by separase." (Office Action, page 3). This represents an improper attempt to shift the initial burden to the Applicants to prove that the invention *is* enabled. In order to establish a *prima facie* case of lack of enablement, however, the initial burden lies with the Examiner to explain why the claimed invention is *not* enabled. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Simply arguing that the prior art does not provide definitive proof for the enablement of the full scope of the currently claimed methods falls far short of establishing a *prima facie* case of non-enablement. In any event, the Examiner's assertion with regard to the teachings in the art clearly does not take into account the successful results reported by Smith *et al.* and Cryns *et al.* for screening and identifying protease substrates.

Finally, with respect to enablement, the Examiner stated that:

> The Examiner takes the position that trial and error experimentation used for searching and screening for specific peptides comprising EXXR, where such peptides are not limited by amino acid

> composition and number of residues, must be performed to ascertain which peptides are substrates for separase. In absence of any guidance and prediction from the specification and the art, this experimentation is undue and is outside the realm of routine experimentation.

(Office Action, page 3). This is merely a conclusory statement that is unsupported by any evidence. In particular, the Examiner has not provided any support for the contention that screening for peptides that contain the separase cleavage motif EXXR and are capable of being cleaved by active separase would have been considered "undue experimentation" from the perspective of a person of ordinary skill in the art.

In addition, the Examiner is respectfully reminded that "[t]he test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). The evidence of record strongly suggests that screening for EXXR-containing peptides for use as separase substrates in the context of the currently claimed methods would have been a matter of routine experimentation. For Example, as noted in Applicants' previous replies:

- Techniques for producing *thousands* of peptides having different amino acid sequences were routine in the art at the time of the effective filing date of the present application (*see* Supplemental Reply filed on June 14, 2005, pages 5-6). Thus a skilled person could have easily generated a multitude of EXXR-containing peptides of varying lengths and amino acid compositions that could then have been tested for their ability to be cleaved by active separase;

- The specification teaches methods that can be used to screen numerous peptides for their ability to be cleaved by separase (*see* Supplemental Reply filed on June 14, 2005, pages 6-7). It follows that a skilled person could have easily distinguished EXXR-containing peptides that are capable of being cleaved by active separase from those that are not cleaved;
- Smith *et al.* demonstrated a protease substrate screening method that uses bacteriophage-based peptide display libraries (*see* Reply Under 37 C.F.R. § 1.111 filed on February 9, 2006, page 5); and
- Cryns *et al.* set forth a method that was used to identify caspase substrates using labeled protein pools that had been transcribed/translated *in vitro* (*see* Reply Under 37 C.F.R. § 1.111 filed on February 9, 2006, page 5).

Thus, taken together, the teachings of the specification and the evidence of record strongly indicates that screening for and identifying EXXR-containing peptides that are capable of being cleaved by active separase would have been routine to persons of ordinary skill in the art. By contrast, no evidence has been put forth to suggest the opposite.

In view of the foregoing, Applicants respectfully submit that the evidence of record strongly supports the enablement of the currently claimed methods and that the Examiner has not established a *prima facie* case of lack of enablement. Accordingly, Applicants respectfully request that the enablement rejection be reconsidered and withdrawn.

B. Written Description

Claims 1-5 and 11-15 were rejected under 35 U.S.C. § 112, first paragraph, for lack of adequate written description. (Office Action, page 3). According to the Examiner, the specification does not provide written description support for "the genus of peptides

containing EXXR, SEQ ID NO: 9, SEQ ID NO: 11, or SEQ ID NO: 12." (Office Action, page 4). Applicants respectfully traverse this rejection for the reasons set forth in the previous responses and provide the following additional remarks.

As noted in Applicants' previous responses, the current case law on written description and the USPTO's own guidelines strongly support Applicants' position that the subject matter of the present claims is more than adequately described. For example, the Federal Circuit indicated in *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 U.S.P.Q.2d 1385, 1389 (Fed. Cir. 2003) that generic elements of a claim that are not themselves the point of novelty of an invention and whose recitation conveys sufficient distinguishing characteristics concerning their identity are adequately described by their recitation alone. The expression "separase substrate comprising an amino acid sequence EXXR" does not refer to new or unknown biological material and readily conveys distinguishing information concerning the identity of the substrates. Thus, under *Amgen* it must be concluded that the substrates used in the practice of the currently claimed methods are more than adequately described by the present specification. The Examiner has failed to explain why the decision in *Amgen* does not support the written description of the present claims.

The general approach to the written description inquiry set forth in *Amgen* has recently been confirmed by the Federal Circuit. For instance, in *Capon v.* Eshhar, 418 F.3d 1349, 1358, 76 U.S.P.Q.2d 1078, 1084-85 (Fed. Cir. 2005), the Federal Circuit held that, in the context of claims to chimeric genes comprising *known* genetic elements, it was unnecessary for the applicants/patentees to provide a structural description (*i.e.*, a recitation of the nucleotide sequence) of the claimed chimeric genes. *See id.*, 418 F.3d at 1358, 76

U.S.P.Q.2d at 1084-85. According to the court, "[w]hen the prior art includes the nucleotide information [of the component DNAs], precedent does not set a *per se* rule that the information must be determined afresh." *Id.* This rationale was further endorsed in the recent case of *Falkner v. Inglis*, 448 F.3d 1357, 2006 U.S. App. LEXIS 13127 (Fed. Cir. May 26, 2006) ("it is the binding precedent of this court that *Eli Lilly* does *not* set forth a *per se* rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art.") Applied to the circumstances of the present claims, *Capon* and *Falkner* strongly support Applicants' position that the genus of separase substrates recited in the claims is more than adequately described by virtue of the fact that molecules identified as separase substrates in the present application were known in the prior art.

It was also noted in Applicants' previous response that the analysis set forth in Example 18 of the USPTO's "Synopsis of Application of Written Description Guidelines" strongly supports Applicants' contention that the genus of separase substrates recited in the present claims is more than adequately described. In reply, the Examiner stated that this Example:

> is not directed to an assay method using a genus of substrates comprising the amino acid sequence EXXR. Example 18 is only directed toward a method of expressing a protein of interest in *Neurospora crassa* mitochondria.

(Office Action, page 4). The Examples from the USPTO's Guidelines, however, are intended to illustrate *general principles* to be applied in a *wide range of circumstances*. Clearly, it was not the intent of the drafters of these Examples to have them apply only to the

narrow circumstances set forth in these hypothetical scenarios. Applicants respectfully submit that it is improper for the Examiner to refuse to consider the guidance provided by the USPTO's own training materials simply because the facts and circumstances of Example 18 do not precisely match the facts and circumstances surrounding the present claims.

As explained in Applicants' previous response, one of the principles taught in Example 18 is that the written description inquiry should focus on the novel aspects of the invention (*e.g.*, the process steps of the claimed method) rather than on elements of the claims that do not represent a point of novelty of the invention (*e.g.*, a nucleic acid that encodes a protein of interest). (*See* Reply Under 35 U.S.C. § 1.111 filed on February 9, 2006, page 13). This general principle, when applied to the present claims, strongly supports Applicants' position that the subject matter of the present claims is more than adequately described.

The Examiner, in justifying the written description rejection, has also made comments similar to those presented in support of the enablement rejection. In particular, the Examiner stated that:

> The specification does not disclose how the length or the composition of the peptide containing EXXR would affect the ability of the separase to recognize and hydrolyzes the peptide. The specification does not disclose where the EXXR should be in relation to the N- or C-terminal of the peptide which will enable the separase to recognize and hydrolyze the peptide. It is not clear from the specification if large peptides comprising EXXR would be hydrolyzed by separase since the specification discloses that small peptides consisting of SEQ ID NO:9, SEQ ID NO: 11, or SEQ ID NO: 12 were found to be separase substrates.

(Office Action, page 4). As explained above, these statements are insufficient to support the enablement rejection; likewise, these conclusory arguments fall far short of satisfying the Examiner's initial burden of establishing a rejection for lack of adequate written description under § 112, first paragraph.

For instance, with regard to the Examiner's statements regarding the length of the substrates and the location of the EXXR sequence, there is no evidence of record to suggest that determining the appropriate size of a separase substrate or the relative orientation of the EXXR sequence within the substrate would have entailed anything more than the application of routine techniques. Without presenting any evidence to indicate that the size of the substrate or the position of the EXXR motif within the substrate would in any way influence the ability of the substrate to be cleaved by active separase, the Examiner has not met his burden in establishing a *prima facie* case of lack of adequate written description.

Also, as noted above, the Examiner's statement that "[i]t is not clear from the specification if large peptides comprising EXXR would be hydrolyzed by separase," fails to take into account the fact the specification provides working examples illustrating the cleavage of SCC1 (a full-length protein containing the EXXR motif) by separase.

Since the case law and the USPTO's Guidelines strongly support Applicants' position that the subject matter of the present claims is more than adequately described, and since the Examiner has not established a *prima facie* case of lack of adequate written description, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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